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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,931	HELLMAN ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,8,25 and 26* is/are rejected.

7)☒ Claim(s) *5,8,25 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicants' response to the Office Action mailed December 17, 2002 (Paper #21-filed 3/17/03) is acknowledged. In response to Amendment-G filed therein, claims 25 and 26 have been amended. Claims 5, 8, 25, and 26 are currently under consideration.

OBJECTIONS MAINTAINED

Drawings

2. The drawings in this application remain objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the examiner allows the application.

Applicant has deferred corrective action until allowance.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form PTO-1449 have cited the references they have not been considered.

Applicant has not addressed the instant objection, accordingly it is maintained.

Claim Objections

4. Claims 5, 8, 25, and 26 are objected to because of the following informalities: The dependent claims do not reference a previous claim. See MPEP 608.01(n). Appropriate correction is required.

The objection is maintained until the claims are renumbered once allowable subject matter is established.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 5, 8, 25, and 26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 25 and 26 are vague and indefinite because it is not clear what the monoclonal antibody will bind. As recited the monoclonal antibody is directed to any composition comprising the entire seq. Id. no.2 (lines 1-8 in the claims), monoclonal antibodies which bind fragments from amino acid position 7 to position 30 of seq. Id. no.2, and monoclonal antibodies which bind fragments from amino acid position 6 to position 30 of seq. Id. no.2. It is not clear if applicant intends the monoclonals of the instant invention to binding the full sequence of seg. Id. no.2 or fragments thereof?

The disclosure has support for Seq. Id. No.2, but does not clearly identify what is considered fragments that *span* position 6 to 30 with gamma-carboxylated glumatic acid positions 17, 21, and 24. In order to clearly identify the instantly claimed fragments, it is suggested that monoclonals of this type include Atcc deposit/accession numbers or seq. Id. nos. for proper identification. Please identify applicants intended meaning/define.

Response to Arguments

Applicants have amended the claims to more clearly identify the binding characteristics of the claimed antibodies. However the claim claims remain unclear because as amended the antibodies are directed to "specific epitopes", while no such specific epitopes are defined by the claims nor the specification. Fragments spanning amino acid position 6 to 30 of seq id no.2 are recited in the claims, however it is not clear if applicant intends the fragments to be specific epitopes. Clarification is required.

Applicant contends that the claims set forth monoclonal antibodies, which bind human carboxylated osteocalcin fragments. This argument was carefully considered, but not found persuasive because the claims appear to indicate amino acids spanning position 6 to 30 of sequence identification number 2. In order to clearly identify the intended binding entity as human-carboxylated osteocalcin fragments, it is suggested that the claims be written to recite human gamma-carboxylated osteocalcin fragments of Seq. Id. No. 2. (Wherein fragments from amino acids position 7 to position 30 of seq. id. no.2, and monoclonal antibodies, which bind from amino acid position 6 to position 30 of seq. id. no. 2 are not required). The rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5, 8, 25, and 26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8 and therefore the written description is not commensurate in scope with the claims drawn to any monoclonal antibody that binds Seq. Id. No.2 (recited in independent claims 4 and 6). See pages 16-22. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is several from its enablement provision (see page 115).

With the exception of Mab's 2H9, 6F9, 3G8, 1C4, and 3H8, the skilled artisan cannot envision the detailed structure of the encompassed monoclonal antibodies and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The monoclonal antibody itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of a compound/seq.id/etc. by only their functional activity does not provide an adequate written description of the genus.

The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus.

At section B(1), the court states that "An adequate written description ...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention" There is insufficient description in the disclosure to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only the isolated Mab's 2H9, 6F9, 3G8, 1C4, and 3H8, but not any monoclonal that competes with the monoclonal antibodies would meet the full breadth of the claims as required by the written description provision of 35 USC 112, first paragraph.

7. Claims 5, 8, 25, and 26 (previously 4-6 and 8-11) remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification lacks complete deposit information for the deposit of monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8.

Because it is not clear that the properties of monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production monoclonal antibodies, one of ordinary skill in the art could be assured to the ability to practice the invention as claimed. Exact replication of the monoclonal antibodies is an unpredictable event.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required. If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required.

Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record that has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository.

The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1)The name and address of the depository;

2)The name and address of the depositor;

3)The date of deposit;

4)The identity of the deposit and the accession number given by the depository;

5)The date of the viability test;

6)The procedures used to obtain a sample if the test is not done by the depository; and

7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

Response to Argument

Applicant contends that the specific monoclonal antibodies taught in the disclosure are fully representative of the claimed genus. Further the claim amendments help to point out that the members of the claimed genus of monoclonal antibodies and antibody fragments are not merely defined by functional activity.

In response, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., The monoclonals taught in the disclosure are recited in the instant claims) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Also the antibodies have not been deposited, therein one of ordinary skill in the art could be assured to the ability to practice the invention as claimed. Exact replication of the monoclonal antibodies is an unpredictable event. Accordingly the deposit is required to practice the instant invention.

Applicant argues that monoclonal antibodies have a well-documented, and highly specific, structure. And the instant antibodies have been defined by the epitope to which it binds (function). Accordingly the invention meets the requirements of written description. This argument was carefully considered but not found persuasive because even though monoclonal antibodies can be readily produced, the total characterization of a monoclonal antibody is a long and complex procedure; which varies widely with the intended use of the antibody.

A general point is that if a single hybridoma has been produced and is intended for a specific function it is unlikely that the antibody produced will have all the required characteristics (Campbell, Laboratory Techniques, Vol. 13, 1984).

Campbell teaches that it is a waste of both reagents and time to attempt full characterization of an antibody, which is not obtained from a fully cloned cell line. See Chapter 10, specifically page 186. While the specification provides enough information for one of ordinary skill in the art to produce hybridoma cell lines secreting antibodies with the same or similar properties as monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8, reproduction of an identical cell line and antibody is an extremely unpredictable event (see Campbell above), and because the specification lacks complete deposit information for the deposit of the hybridoma cell line(s) secreting monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8, it does not appear that monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because certain of the claims specifically require the use of monoclonal antibodies 2H9, 6F9, 3G8, 1C4, and 3H8, a suitable deposit of the hybridoma cell lines for patent purpose is required.

Applicant has directed Examiner to the recent case of Enzo Biochem, Inc v. Gene-probe Inc. citing that the known structure and existence of a specific epitope is sufficiently descriptive. This argument was carefully considered but not found persuasive because Enzo provided reduction to practice and deposited the derived biological materials, thereby demonstrating "possession" of the invention. Applicant has not deposited the instantly claimed monoclonals, therein "possession" with respect to written description has not been meet.

Applicant contends the issue of adequate written description is dependent on the facts of each individual case and the mere citation of case law for certain broad propositions cannot be taken out of context of the specific case. Further the presently claimed invention is directed to a monoclonal antibody or recombinant fragment, which binds a specific epitope.

This argument was carefully and fully considered but not found persuasive because the rejection was based on the facts of this individual case supported by the cited case law. The instant application being directed to monoclonal antibodies and their utility lacks written description and lack enablement because the particular inventive monoclonal antibodies have not been deposited.

Therein one of ordinary skill in the art could not be assured to the ability to practice the invention claimed. Exact replication of the monoclonal antibodies of the instant invention is an unpredictable event. The rejections are maintained.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 5, 8, 25, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurihara et al. (US Patent #5,164,483).

Kurihara et al. teach the production of osteocalcin having either of glutamic acid or γ-carboxyglutamic acid at residue 17 and γ-carboxyglutamic acid at residues 21 and 24. Column 3lines 48-63. The peptides are utilized to generate specific antibodies for human circulating osteocalcin measurements. (for example see column 2, lines 42-56; column 9 line 47 to column 12). Note, the Patent and Trademark Office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference, in the first, place between reagents of the prior art and those instantly disclosed and, that if there is such a difference, that such a difference would have been considered unexpected, i.e. unobvious, by one of ordinary skill in the art. The burden is upon applicant to present such factual evidence. See e.g. In re Best (195 USPQ 430(CCPA 1977)) or Ex parte Phillips (28 USPQ2d 1302 (BPAI 1993)).

II. Claims 5, 8, 25, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Hosoda et al. (US Patent #5,506,111).

Hosoda et al. teach the production of antibodies to osteocalcin fragments, and in particular fragments of osteocalcin having residues 1-20 with glutamic acid at residue 17 or having residues 43-49 or having residues 36-49 (column 12-16 and 20-24, and figures 1-3), and the utility of said antibodies in immunoassays for determining osteocalcin. The antibodies specific for residues 1-20 of Glu ^{17}-osteocalcin taught by the reference would inherently bind osteocalcin as instantly disclosed and claimed (open language - having 6-30 or 7-30).

Moreover, antibodies specific for residues 43-49 or residues 36-49 of osteocalcin would inherently bind to osteocalcin having Glu ^{17} and/or Gla ^{21} and/or Glu^{21} and/or Gla ^{24} and/or Glu^{24}. Gamma carboxylation at various sites is discussed in column 2 line 55 to line 65 and column 3 lines 47-55. Note, the Patent and Trademark Office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference, in the first, place between reagents of the prior art and those instantly disclosed and, that if there is such a difference, that such a difference would have been considered unexpected, i.e. unobvious, by one of ordinary skill in the art. The burden is upon applicant to present such factual evidence. See e.g. In re Best (195 USPQ 430(CCPA 1977)) or Ex parte Phillips (28 USPQ2d 1302 (BPAI 1993)).

9. For reasons aforementioned, no claims are allowed.

Remarks

10. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Hellman et al. (Journal of Bone Mineral Research, Vol.11., No.8., 1996, pages 1165-1175) disclose nine monoclonal antibodies against osteocalcin via two-site assay procedures.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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6/2/03

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